

REMARKS

Claims 1-4 are pending in the application. No new matter has been inserted into the application.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1-4 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

That endostatin is a widely known inhibitor of angiogenesis is undisputed. The Examiner acknowledges this in the Office action at pages 5 and 6. However, until Applicants' disclosure in the present application, the mechanism of endostatin action was unclear. In the present application, Applicants have for the first time demonstrated that the mechanism by which endostatin inhibits angiogenesis is by binding to vitronectin, which results in preventing vitronectin from binding to the cell surface receptor $\alpha V\beta 3$, which is a necessary mediator for angiogenesis to occur. Further, Applicants have demonstrated that endostatin binds to the GRGDS motif of vitronectin.

Since endostatin is a well-known angiogenesis inhibitor, and its mechanism of action has now been newly revealed, Applicants assert that a molecule that mimics the activity of endostatin, i.e., a compound that binds to the GRGDS motif of vitronectin, would logically also inhibit angiogenesis. The Examples in the present application show that suramin, quisqualic acid, D-cycloserine, L-histidine have been identified as endostatin mimics as they bind to the GRDGS motif of vitronectin.

Applicants submit that the Examiner has failed to establish a *prima facie* case of non-enablement of the present invention. The Examiner has failed to set forth any reason why a person of ordinary skill in the art would not be able to practice the present invention given the disclosure in the present application.

When rejecting a claim under the enablement requirement of section 112, the Examiner bears the “initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification.” *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *Id.*; and MPEP § 2164.04.

Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). The burden placed on the Examiner is reflected in the MPEP § 706.03.

Accordingly, the case law makes clear that properly reasoned and supported statements explaining any failure to comply with Section 112 are a requirement to support a rejection. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Examiner has failed to establish why the mimics would not work to reduce or prevent angiogenesis especially given that Applicants have for the first time demonstrated the *modus operandi* of a well-known angiogenesis inhibitor. Applicants have provided mimics that can be used in the same manner as endostatin to reduce or prevent angiogenesis. In the absence of such evidence or scientific reasoning, Applicants submit that the present application must be

considered enabling for the full scope of the claims. Removal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103(a) over Chugai Seiyaku Kabushiki Kaisha (GB 1,153,113)

Claims 1-4 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chugai Seiyaku Kabushiki Kaisha. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Chugai ‘113 discloses the use of cycloserine to increase anti-tumor activity and reducing the toxicity of hemolytic streptococci. Applicants disagree with the Examiner’s position that Chugai ‘113 renders the claimed invention obvious. However, in order to expedite the prosecution of the application, “cycloserine” has been deleted from the claims. Accordingly, it is believed that this rejection has been overcome.

Rejection Under 35 U.S.C. §103(a) over Slusher et al. (WO 97/48409)

Claims 1-4 have been rejected under 35 U.S.C. §103(a) over Slusher et al. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

Slusher ‘409 generally discloses N-Acetylated α-Linked Acidic Dipeptidase (NAALADase) inhibitors. Slusher ‘409 exemplifies 2-(phosphonomethyl) pentanedioic acid in a tumor reduction assay and further discusses quisqualic acid in terms of a NAALADase inhibitor. Table IV in Slusher ‘409 shows quisqualic acid in a 3H-Thymidine incorporation assay on a prostate cancer cell line.

Applicants note that the presently claimed invention is directed to an angiogenesis inhibition protocol. The experimental evidence using quisqualic acid provided in Slusher ‘409 is

limited to its effect on a cell line, which does not provide enough of the necessary teaching for use in inhibiting angiogenesis or tumorigenesis. In contrast, Applicants have determined a pathway for inhibiting tumorigenesis by blocking angiogenesis. Thus, Slusher '409 fails to be an enabling reference in regards to treating the angiogenesis related diseases as indicated in the presently claimed invention. Accordingly, the presently claimed invention is not obvious over Slusher '409.

Conclusion

It is believed that the application is now in condition for allowance. Applicant requests the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. 502486 for any fees required under 37 CFR §§1.16 and 1.17 that are not covered, in whole or in part, by a credit card payment enclosed herewith and to credit any overpayment to said Deposit Account No. 502486.

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Respectfully submitted,

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